IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

IOVATE HEALTH SCIENCES U.S.A., INC., et al. Plaintiffs, v. WELLNX LIFE SCIENCES INC., et al. Defendants.	C.A. No. 07-286-JJF

UNOPPOSED MOTION FOR LEAVE TO FILE FIRST AMENDED COMPLAINT

1. Plaintiffs Iovate Health Sciences U.S.A., Inc. ("Iovate U.S.A."), Iovate Health Sciences International, Inc. ("Iovate International"), and Iovate T & P, Inc. ("Iovate T & P") ("Plaintiffs"), hereby move for leave to file the attached First Amended Complaint, pursuant to Federal Rule of Civil Procedure 15(a) and Local Rule 15.1. This motion is unopposed by defendants.

2. The Scheduling Order in this action (D.I. 32) as amended by stipulation dated January 18, 2008 (D.I. 34) sets forth a deadline of January 25, 2008 for motions to amend the pleadings.

3. Pursuant to D. Del. Local Rule 15.1: (a) the proposed First Amended Complaint, complete with handwritten signature, is attached hereto as Exhibit 1; and (b) a blackline version of the proposed First Amended Complaint, which indicates in what respects it differs from the original Complaint (D.I. 1) via striking through materials to be added and double underlining materials to be added, is attached hereto as Exhibit 2.

4. On May 24, 2007, Plaintiffs brought this suit against Defendants WellNx Life Sciences Inc. ("WellNx") (d/b/a NV Inc.), NxCare Inc. ("NxCare"), NxLabs Inc. ("NxLabs"),

Biogenetix, Slimquick Laboratories ("Slimquick"), Derek Woodgate and Bradley Woodgate (collectively "Defendants") alleging infringement of U.S. Patent Nos. 5,973,199, 6,716,459 and 5,968,900 (*see* D.I. 1).

5. WellNx, NxCare Inc., NxLabs, Slimquick and Biogenetix responded to the Complaint on July 16, 2007 and asserted counterclaims for non-infringement, invalidity and patent misuse of U.S. Patent Nos. U.S. Patent Nos. 5,973,199, 6,716,459 and 5,968,900 (*see* D.I. 17); and Defendants Derek and Bradley Woodgate moved to dismiss for lack of personal jurisdiction (*see* D.I. 13). Plaintiffs responded to the counterclaims on August 13, 2007 (*see* D.I. 24).

6. After further discovery in this action, Plaintiffs wish to remove Slimquick Laboratories as a Defendant to this action, remove Flamma SpA and Use Techno Corporation as plaintiffs, remove its allegation of infringement under U.S. Patent No. 6,716,459 and add a count of infringement under U.S. Patent No. 6,277,396.

7. The Federal Rules contemplate the liberal amendment of pleadings. *See* Fed. R. Civ. P. 15(a) (stating that leave to amend the pleadings "shall be freely given when justice so requires"). In the absence of a specific reason to deny a motion to amend—e.g., undue delay, bad faith, undue prejudice to the nonmoving party, futility of the amendment—such motions are granted as a matter of course. *See e.g., Foman v. Davis*, 371 U.S. 178, 182 (1962).

WHEREFORE, in view of the foregoing, Plaintiffs respectfully request that the Court enter an Order in the form attached hereto, granting Plaintiffs leave to file and serve the "First Amended Complaint" attached hereto as Exhibit 1.

YOUNG CONAWAY STARGATT & TAYLOR LLP

/s/ Karen L. Pascale

January 25, 2008

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CERTIFICATE OF SERVICE

I, Karen L. Pascale, Esq., hereby certify that on January 25, 2008, the foregoing document was electronically filed with the Clerk of the Court using CM/ECF, which will send notification that such filing is available for viewing and downloading to the following counsel of record:

Mary B. Graham, Esq. *[mgraham@mnat.com]*
Rodger D. Smith, II, Esq. *[rsmith@mnat.com]*
James W. Parrett, Jr., Esq. *[jparrett@mnat.com]*
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Additionally, I hereby certify that the foregoing document was served by hand-delivery and e-mail upon the above-listed counsel and on the following counsel as indicated.

BY E-MAIL

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/s/ Karen L. Pascale

January 25, 2008

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IN THE UNITED STATES DISTRICT COURT

FOR THE DISTRICT OF DELAWARE

IOVATE HEALTH SCIENCES U.S.A., INC., et al. Plaintiffs, v. WELLNX LIFE SCIENCES INC., et al. Defendants.	C.A. No. 07-286 JJF JURY TRIAL DEMANDED

FIRST AMENDED COMPLAINT

Plaintiffs Iovate Health Sciences U.S.A., Inc. ("Iovate U.S.A."), Iovate Health Sciences International, Inc. ("Iovate International"), and Iovate T & P, Inc. ("Iovate T & P") (collectively "Iovate" or "Plaintiffs"), hereby allege for their Complaint against WellNx Life Sciences Inc. ("WellNx") (d/b/a NV Inc.), NxCare Inc. ("NxCare"), NxLabs Inc. ("NxLabs"), Biogenetix, Derek Woodgate and Bradley Woodgate (collectively "Defendants"), on personal knowledge as to their own activities and on information and belief as to all other matters, as follows:

PARTIES

1. Iovate U.S.A. is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 3880 Jeffrey Boulevard, Blasdell, New York, NY, 14129.

2. Iovate International is a corporation organized and existing under the laws of Ontario, Canada, with its principal place of business at 381 North Service Road West, Oakville, ON, Canada,L6M 0H4.

3. Iovate T & P is a corporation organized and existing under the laws of Ontario, Canada, with its principal place of business at 381 North Service Road West, Oakville, ON, Canada, L6M 0H4.

4. Upon information and belief, Defendant WellNx is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9, and/or 218 Silvercreek Parkway, Guelph, ON, Canada.

5. Upon information and belief, Defendant NxCare is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

6. Upon information and belief, Defendant NxLabs is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

7. Upon information and belief, Defendant Biogenetix is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

8. Upon information and belief, Defendants Derek Woodgate and Bradley Woodgate are individuals and the founders of WellNx, (and its predecessor entities) NxCare, NxLabs, Biogenetix, and are officers, shareholders, and/or directors of WellNx, NxCare, NxLabs, Biogenetix, and personally direct and control the activities herein complained.

9. Upon information and belief, Defendant Derek Woodgate resides at 1594 Waldie Avenue, Milton, ON, Canada, L9T 5K8.

10. Upon information and belief, Defendant Bradley Woodgate resides at 803-373 Front Street West, Toronto, ON, Canada, M5V-3R7.

JURISDICTION AND VENUE

11. This is an action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code. Accordingly, this Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338.

12. Venue is proper in this Court pursuant to 28 U.S.C. §§ 1331, 1391(b), 1391(d) and 1400.

13. Upon information and belief, Defendant WellNx maintains an office at 1201 N. Orange Street, Suite 741, Wilmington, DE, 19801.

14. Upon information and belief, Defendant NxCare maintains an office at 874 Walker Rd., Dover, DE, 19904.

GENERAL ALLEGATIONS

15. On October 26, 1999, United States Patent No. 5,973,199 ("the '199 patent"), titled "Hydrosoluble Organic Salts of Creatine," was duly and legally issued by the United States Patent and Trademark Office. A true and correct copy of the '199 patent is attached as Exhibit A of this Complaint.

16. Iovate Health Sciences U.S.A., Inc. is the owner through assignment of the '199 patent.

17. On October 19, 1999, United States Patent No. 5,968,900 ("the '900 patent"), titled "Increasing Creatine and Glycogen Concentration in Muscle," was duly issued by the United States Patent and Trademark Office. A true and correct copy of the '900 patent is attached as Exhibit B of this Complaint.

18. Iovate T & P is the owner of all rights, title and interest in and to the '900 patent.

19. On August 21, 2001, United States Patent No. 6,277,396 ("the '396 patent"), titled "Dietary Supplement Containing a Thermogenic Substance and an Adrenal Support Substance," was duly and legally issued by the United States Patent and Trademark Office. A true and correct copy of the '396 patent is attached as Exhibit C of this Complaint.

20. Iovate T & P is the owner through assignment of the '396 patent.

21. Upon information and belief, Defendants have made, used, offered for sale, sold and/or imported nutritional supplements, including, Vaso, Vaso XP, Hyper Growth, Lean Hyper Growth, Muscle Expansion Pack, Pump System, Creatine-D^{2}T, REVxp Hardcore, Methyl Ripped, Ripped System and/or NV throughout the U.S. and in this judicial district.

22. The supplement information for Vaso lists "Tri-creatine malate."

23. The supplement information for Vaso XP lists "Tri-creatine malate."

24. The supplement information for Hypergrowth lists 10 grams of creatine derivatives (micronized creatine monohydrate, tricreatine malate and buffered creatine), and "InsuTech." "Each serving of Hypergrowth delivers 10g of CreaPlex3 . . . for maximum creatine absorbtion and retention."

25. The supplement information for Lean Hypergrowth lists 10 grams of creatine derivatives (micronized creatine monohydrate, tricreatine malate and buffered creatine) and "InsuTech."

26. The supplement information for Muscle Expansion Pack (Anavol, Vaso) lists "Tri-creatine malate."

27. The supplement information for Pump System (Vaso, Plasmavol, NO Surge) lists "Tri-creatine malate."

28. The product label for Creatine-D^{2}T lists 4000 mg of Creatine derivatives (Creatine Ethyl Ester, Creatine AKG, and Creatine Decanoate) per serving, and an "Insulin Signaling Complex".

29. The supplement information for REVxp Hardcore lists caffeine anhydrous, 70 % total catechins, ginsing, and 4-hydroxyisoleusine (from fenugreek)(seed).

30. The supplement information for Methyl Ripped lists di-caffeine alpha ketoglutarate, di-caffeine malate, esterified green tea extract (standardized for 45% 45% Epigallocatechin Gallate (EGCG) Ester, 2% Epicatechin Gallate (ECG) Ester, 2% Gallocatechin Gallate (GCG) Ester, 1% Catechin Gallate (CG) Ester), Gugglesterones E&Z HCl, and Ashwagandha.

31. The supplement information for Ripped System (Methyl Ripped, Methyl Dry) lists di-caffeine alpha ketoglutarate, di-caffeine malate, esterified green tea extract (standardized for 45% 45% Epigallocatechin Gallate (EGCG) Ester, 2% Epicatechin Gallate (ECG) Ester, 2% Gallocatechin Gallate (GCG) Ester, 1% Catechin Gallate (CG) Ester), Gugglesterones E&Z HCl, and Ashwagandha.

32. The supplement information for NV lists Green Tea Extract (Leaf)(Standardized for polyphenols and Epigallocatechin Gallate (EGCG)), Panax Ginseng Extract, and Alpha-Lipoic Acid.

FIRST CAUSE OF ACTION
(Infringement of the '199 Patent)

33. Plaintiffs repeat and re-allege the allegations of paragraphs 1-32 of the Complaint as if set forth herein.

34. By their actions, Defendants have infringed and are infringing the '199 patent.

35. Upon information and belief, the infringement by Defendants has been and continues to be willful.

36. As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

SECOND CAUSE OF ACTION
(Infringement of the '900 Patent)

37. Plaintiffs repeat and re-allege the allegations of paragraphs 1-36 of the Complaint as if set forth herein.

38. By their actions, Defendants infringed and are infringing the '900 patent.

39. Upon information and belief, the infringement by Defendants has been and continues to be willful.

40. As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

THIRD CAUSE OF ACTION
(Infringement of the '396 Patent)

41. Plaintiffs repeat and re-allege the allegations of paragraphs 1-40 of the Complaint as if set forth herein.

42. By their actions, Defendants infringed and are infringing the '396 patent.

43. Upon information and belief, the infringement by Defendants has been and continues to be willful.

44. As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for entry of judgment against each Defendant as follows:

A. The Defendants infringe the '199, '900 and '396 patents by their making, using, offering for sale, selling and/or importing nutritional supplements, including Vaso and/or Vaso

XP, Hyper Growth, Lean Hyper Growth, Muscle Expansion Pack, Pump System, Creatine-D^2T, REVxp Hardcore, Methyl Ripped, Ripped System and NV;

B. That Defendants' infringement of the '199, '900 and '396 patents is willful;

C. That Defendants, their officers, directors, affiliates, agents, servants, employees and attorneys, and all those persons acting in privity or in concert with any of them, be preliminarily and permanently enjoining from infringement of the '199, '900 and '396 patents;

D. That Plaintiffs be awarded their damages for infringement of the '199, '900 and '396 patents, and that the damages be trebled;

E. That this case be declared to be exceptional in favor of Plaintiffs under 35 U.S.C. § 285, and that Plaintiffs be awarded their costs, attorneys' fees, and other expenses incurred in connection with this action;

F. That Plaintiffs be awarded such other and further relief as may be appropriate.

DEMAND FOR JURY TRIAL

Plaintiffs demand a trial by jury.

Dated: January 25, 2008

Respectfully submitted,

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EXHIBIT

A

US005973199A

United States Patent [19]

Negrisoli et al.

[11] Patent Number: 5,973,199

[45] Date of Patent: *Oct. 26, 1999

[54] HYDROSOLUBLE ORGANIC SALTS OF CREATINE

[75] Inventors: Gianpaolo Negrisoli; Lucno Del Corona, both of Bergamo, Italy

[73] Assignee: Flamma S.p.A., Bergamo, Italy

[*] Notice: This patent issued on a continued prosecution application filed under 37 CFR 1.53(d), and is subject to the twenty year patent term provisions of 35 U.S.C. 154(a)(2).

[21] Appl. No.: 08/649,620

[22] PCT Filed: Jul. 21, 1995

[86] PCT No.: PCT/EP95/02897

§ 371 Date: May 22, 1996

§ 102(e) Date: May 22, 1996

[87] PCT Pub. No.: WO96/04240

PCT Pub. Date: Feb. 15, 1996

[30] Foreign Application Priority Data

Aug. 4, 1994 [IT] Italy MI94A001693

[51] Int. Cl.[6] C07C 241/00

[52] U.S. Cl. 562/560

[58] Field of Search 562/560

[56] References Cited

U.S. PATENT DOCUMENTS

1,967,400	7/1934	Fischl	562/560
4,420,432	12/1983	Chibata	562/560
5,091,171	2/1992	Yu	424/642
5,387,696	2/1995	Kottenhahn	548/533
5,489,589	2/1996	Wittman	514/232.8
5,627,172	5/1997	Almada	514/120

FOREIGN PATENT DOCUMENTS

0 669 083	8/1995	European Pat. Off. .	
53-6204	3/1978	Japan	562/560
94/02127	2/1994	WIPO .	

OTHER PUBLICATIONS

Chemical Abstracts, vol. 84, No. 1, 1976 Columbus, Ohio, US; p. 13433.

ACTA Physiol. Scand. (1995) , 153 (2), 207–9 Coden: APSCAX: ISSN: 0001–6772, 1995 Earnest, C.P. et al.

Primary Examiner—Michael L. Shippen

Attorney, Agent, or Firm—Griffin, Butler, Whisenhunt & Szipl,

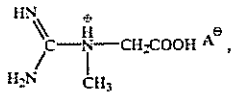
[57] ABSTRACT

Hydrosoluble organic salts of creatine are disclosed. The salts are useful in the dietetic and food industry.

3 Claims, No Drawings

HYDROSOLUBLE ORGANIC SALTS OF CREATINE

The present invention refers to hydrosoluble organic salts of creatine of general formula I:



(I)

wherein $A^{\ominus}$ represents the anion of a mono, bi- or tricarboxylic acid. Preferred anions are the citrate, maleate, fumarate, tartrate or malate.

Creatine or N-(aminoiminomethyl)-N-methylglycine is a sarcosine derivative present in the muscle tissue of many vertebrates, man included, mainly combined with phosphoric acid in form of phosphorylcreatine and it is involved in the energy transfer from mitochondria to the ATP utilization sites.

Several studies indicate that there is a relationship between the creatine (phosphoryl creatine) concentration in the muscles having the function of keeping an high intracellular ATP/ADP ratio and maximum sustainable physical effort (Annu. Rev. Biochem. 54: 831–862, 1985; Science 24: 448–452, 1981; BESSMAN S. P., and F. SAVABI. The role of the phosphocreatine energy shuttle in exercise and muscle hypertrophy. In: Biochemistry of Exercise VII. A. W. Taylow, P. D. Gollnick, H. J. Green, C. D. Ianuzzo, E. G. Noble, G. Metivier, and J. R. Sutton., Intl. Series Sports Sciences 21: 167–178, 1990).

The creatine increase in diets may therefore be useful to bring the plasma creatine concentrations at levels providing significant values of creative itself in the muscle. The short creatine half-life in plasma (1–1.5 hours) makes however necessary to reach rapidly said levels and this, in view of the bioavailability degree of creatine, is obtainable only by the administration of high doses of 5–10 g (for mean body weights of 70 kg), amounts well tolerated because of the lack of toxicity of the compound.

The low solubility of creatine in water (1 g in 75 ml) is therefore a practical limitation to the possibility of marking immediately available in the specific diet the necessary amounts of creatine.

WO 94/02127, published on Feb. 3, 1994, discloses the use of creatine, optional combined with aminoacids or other components, in order to increase the muscle performance in mammals.

The present invention provides hydrosoluble stable organic salts of creatine of formula I characterized by high water solubility (from 3 to 15 times higher them that of creatine itself) and a process for their preparation. The salts of formula I are prepared by salifying creatine with the corresponding acids in aqueous or hydroalcoholic concentrated solution or in a water-immiscible solvent, at temperatures ranging from the room temperature to 50° C., optionally concentrating the solutions and filtering the crystallized salts. According to a preferred embodiment the salts of formula I are prepared by reacting creatine with an excess organic acid in ethyl acetate until the salt is completely formed, detectable with the IR analysis, cooling and filtering. The filtrated solvent, containing the excess acid is recycled and, after filling up of the components, is used for a further reaction.

The salts are characterized by IR, melting point, potentiometric and HPLC assay.

Table 1 reports the solubility of the salts I of the invention.

TABLE 1

Creatine salt	Water solubility % (g/100 ml)
Citrate	10
Maleate	19
Fumarate	3
Tartarate	8,5
Malate	4,5

EXAMPLE 1

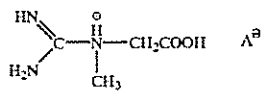
39.45 g (0.18 mol) of monohydrate citric acid are suspended in 100 ml of ethyl acetate. 20 g (0.134 mol) of monohydrate creatine are added to the stirred suspension at 20–25° C. and the mixture is stirred 4 hours at 25° C. After IR control, the product is filtered and washed with ethyl acetate, then dried in oven at 50–55° C., obtaining 90% of salts, m.p. 112–114° C., 99.2% titer.

EXAMPLE 2

14.9 g (0.1 mol) of monohydrate creatine are added to a solution of 11.6 g (0,1 mol) of maleic acid in 20 ml of water. The so obtained solution is concentrated, cooled to 5° C. and the product filtered and dried under vacuum at 50° C., obtaining 87% of salt, m.p. 128–129° C., 99.8% titer.

We claim:

1. An isolated hydrosoluble salt of creatine of the formula:



wherein A^- represents the anion of citric, maleic, fumaric, or malic acid.

2. The hydrosoluble salt of claim 1, wherein A^- is a citrate anion, said salt having a melting point of 112–114° C.

3. The hydrosoluble salt of claim 1, wherein A^- is a maleate anion, said salt having a melting point of 128–129° C.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE

CERTIFICATE OF CORRECTION

PATENT NO. : 5,973,199
DATED : October 26, 1999
INVENTOR(S) : NEGRISOLI et al

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

On the title page item [75], change "Gianpaolo" to --Giampaolo-- and change "Lucno" to --Lucio--.

Signed and Sealed this

Twenty-eighth Day of March, 2000

Attest:

Attesting Officer

Q. TODD DICKINSON

Commissioner of Patents and Trademarks

EXHIBIT

B

US005968900A

United States Patent [19]

Greenhaff et al.

[11] Patent Number: 5,968,900

[45] Date of Patent: Oct. 19, 1999

[54] INCREASING CREATINE AND GLYCOGEN CONCENTRATION IN MUSCLE

[75] Inventors: Paul Leonard Greenhaff, Wollaton; Allison Lesley Green, The Park; Ian Andrew MacDonald, Beeston, all of United Kingdom; Eric Hultman, Stockholm, Sweden

[73] Assignee: The University of Nottingham, Nottingham, United Kingdom

[21] Appl. No.: 08/875,326

[22] PCT Filed: Dec. 15, 1995

[86] PCT No.: PCT/GB95/02933

§ 371 Date: Sep. 29, 1997

§ 102(e) Date: Sep. 29, 1997

[87] PCT Pub. No.: WO96/18313

PCT Pub. Date: Jun. 20, 1996

[30] Foreign Application Priority Data

Aug. 25, 1995 [GB] United Kingdom 9517443

[51] Int. Cl.[6] A61K 38/28; A61K 31/70; A61K 31/715; A61K 31/195

[52] U.S. Cl. 514/3; 514/4; 514/23; 514/53; 514/54; 514/565

[58] Field of Search 514/3, 4, 23, 53, 514/54, 565

[56] References Cited

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0 449 787 2/1991 European Pat. Off. .
WO94/02127 3/1994 WIPO .

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Haider W. Et al., "Improvement of Cardiac Preservation by Preoperative High Insulin Supply," Database Embase, Elsevier Science Publishers, Amsterdam, NL, J. Thorac, Cardiovasc. Surg. (1984).

Samuel P. Bessman, "The Oringin of theCreatine–Creatine Phosphate Energy Shuttle", pp. 75–81, Heart Creatine Kinase–Chapter 7(1980) .

Primary Examiner—Kimberly Jordan
Attorney, Agent, or Firm—Watts, Hoffmann, Fisher & Heinke Co., L.P.A.

[57] ABSTRACT

Compositions herein increased creatine retention and/or glycogen storage in muscle. A composition comprises creatine or its derivative and a carbohydrate or its derivative. The carbohydrate is in an amount by weight which is greater than the amount of creatine. The amount of carbohydrate and the amount of creatine are effective for increasing creatine retention and/or glycogen storage in muscle. The compositions may be in the form of a pharmaceutical or a dietary supplement and are intended for use in the human or animal body. Other compositions comprise creatine or an active derivative together with insulin or an active derivative. The amount of creatine and the amount of insulin are effective for increasing creatine retention and/or glycogen storage in muscle. The compositions including creatine and insulin may further contain a carbohydrate or its derivative. A method of increasing creatine retention in a human or animal body comprises causing an increase in blood plasma creatine concentration and causing a substantially simultaneous increase in blood plasma insulin concentration. A method of increasing glycogen storage in a human or animal body comprises causing an increase in blood plasma creatine carbohydrate concentration and causing a substantially simultaneous increase in blood plasma creatine concentration. The compositions to increase the creatine retention and/or glycogen storage in the muscle are administered by injection or ingestion.

53 Claims, 3 Drawing Sheets

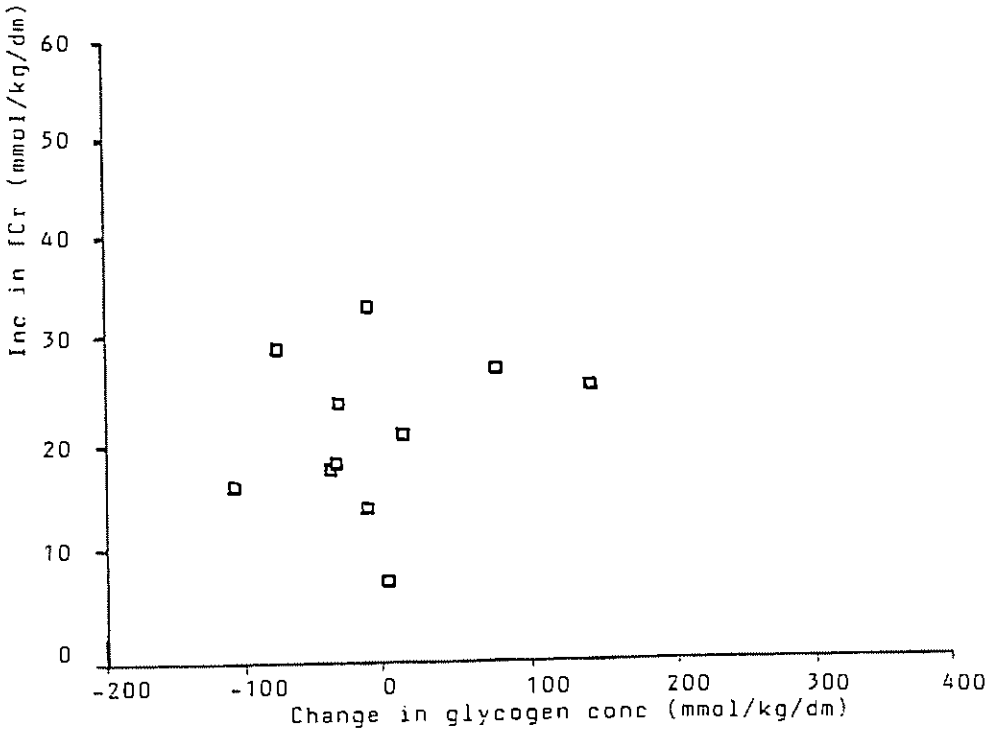

FIGURE 1

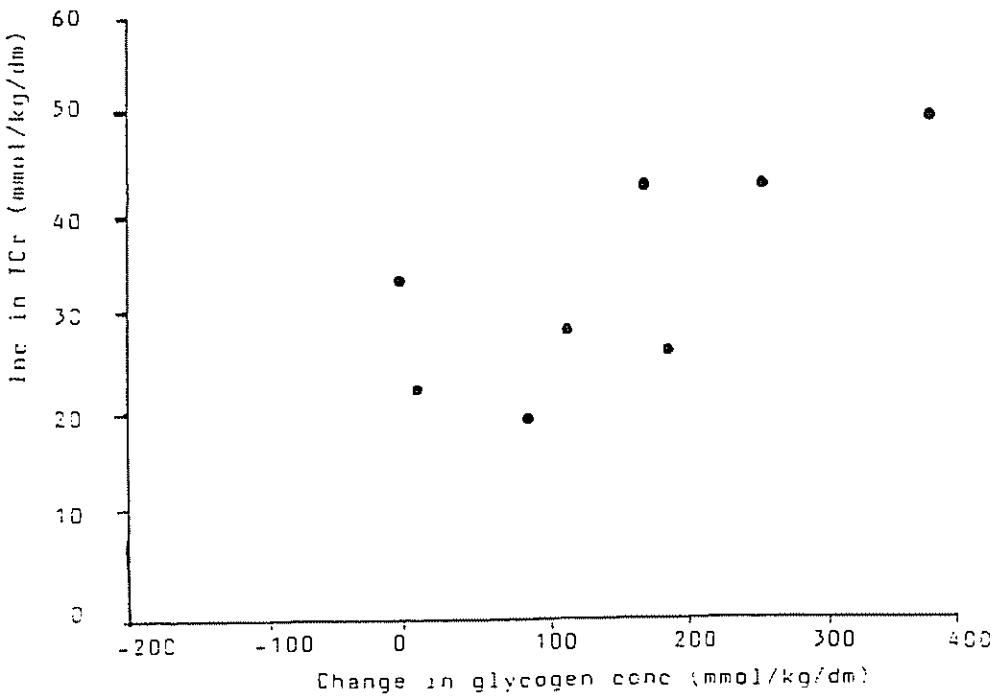

FIGURE 2

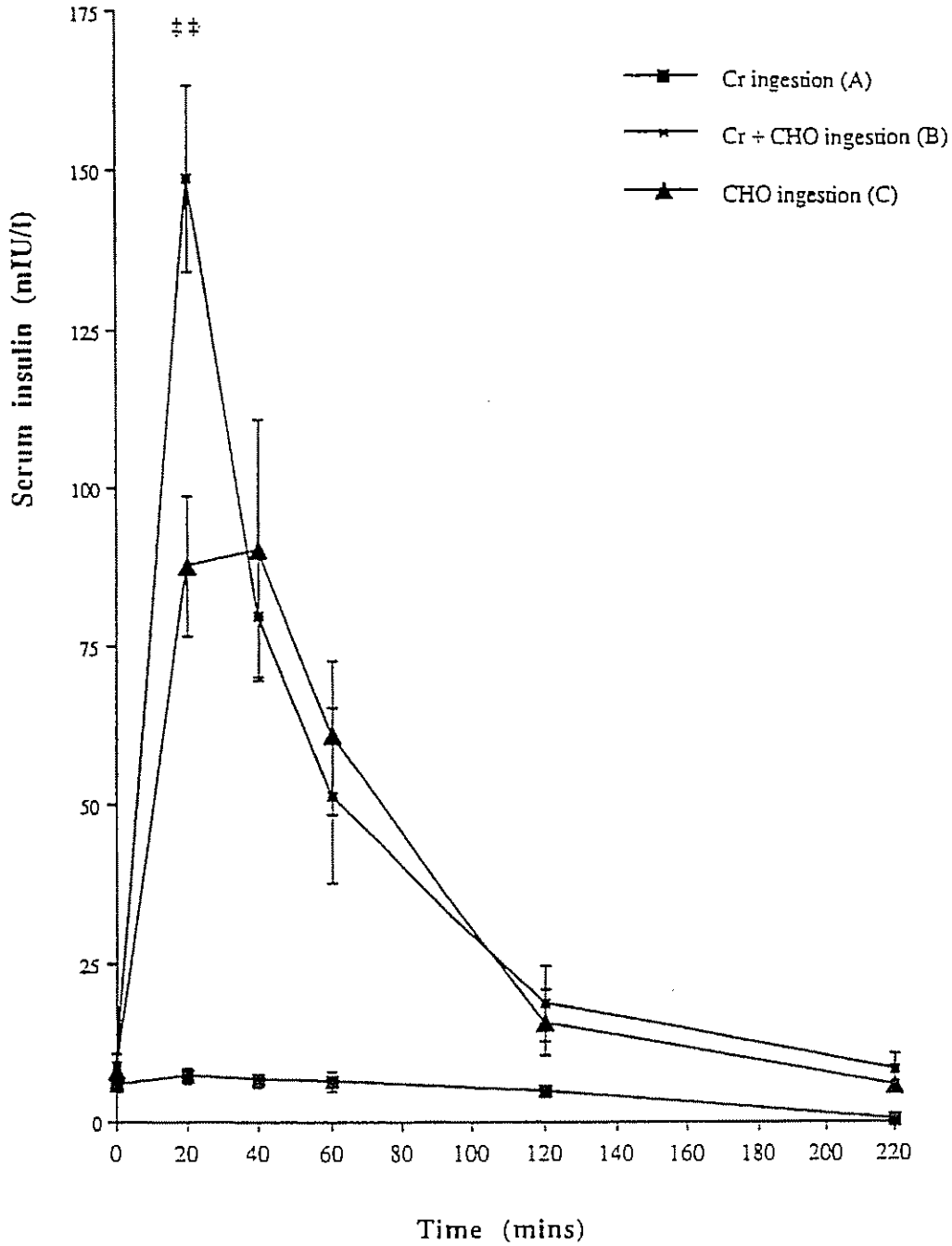
‡‡
Cr ingestion (A)
Cr + CHO ingestion (B)
CHO ingestion (C)
Serum insulin (mIU/l)
175
150
125
100
75
50
25
0
0
20
40
60
80
100
120
140
160
180
200
220
Time (mins)

FIGURE 3

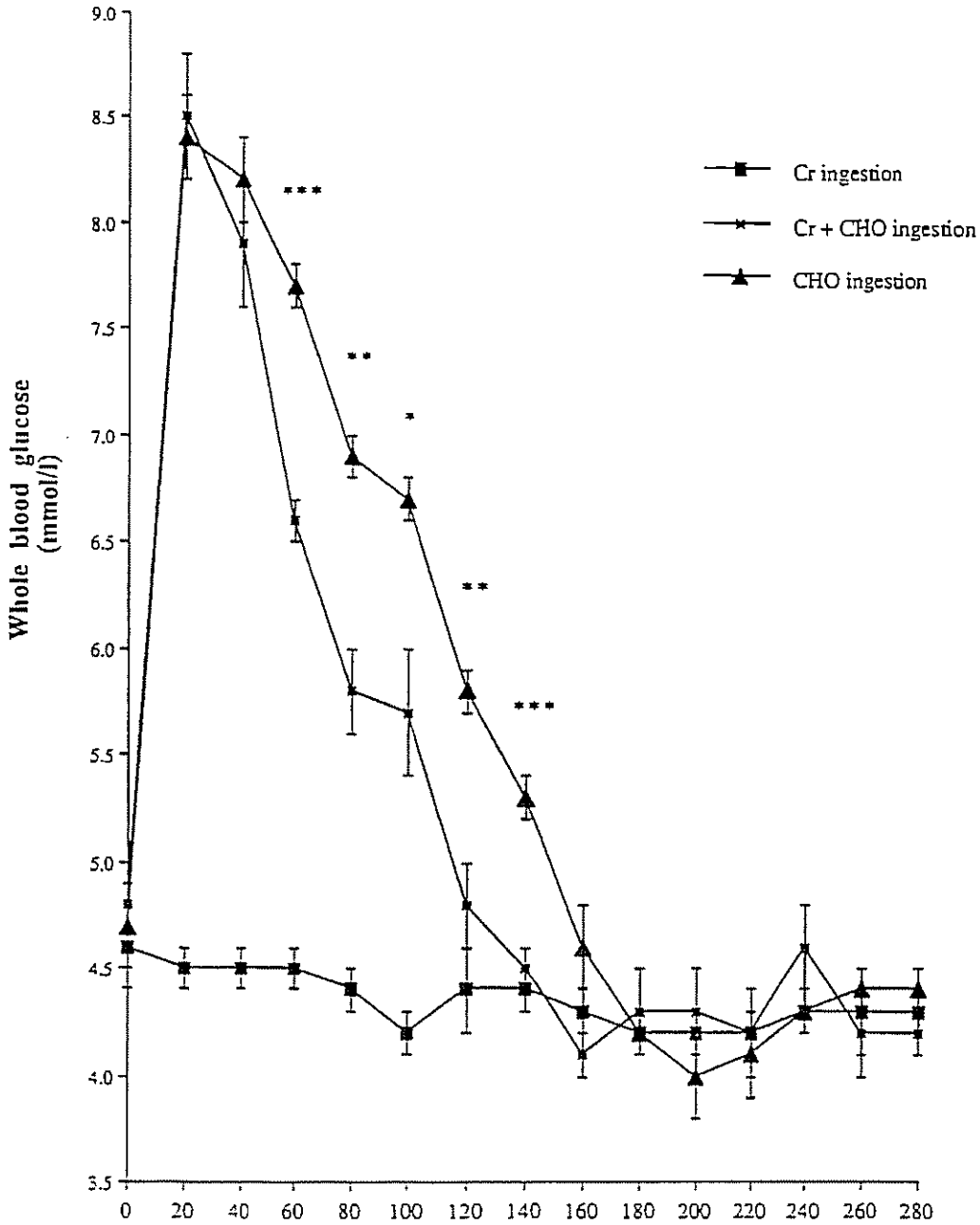
Whole blood glucose (mmol/l)
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
0
20
40
60
80
100
120
140
160
180
200
220
240
260
280
***
**
*
**
***
Cr ingestion
Cr + CHO ingestion
CHO ingestion
Time (mins)

FIGURE 4

INCREASING CREATINE AND GLYCOGEN CONCENTRATION IN MUSCLE

This is a 371 of PCT/6B95/02933, filed Dec. 15, 1995.

The present invention concerns the retention of creatine within the body, and relates in particular but not exclusively to a method and composition for increasing creatine uptake in humans. The invention also concerns a method and composition for simultaneously increasing glycogen concentration in muscle.

Creatine (methylglycocyamine, $H_2NC{=}NH{\cdot}N(CH_3)CH_2CO_2H$) is known to be present in the muscles of vertebrates. It is present in a phosphorylated and a non-phosphorylated form and has been shown to be involved in muscular contraction and the development of fatigue. Creatine is produced naturally by the body, but is also obtained from animal foods.

Most bodily creatine is present in muscle, and it is believed that increasing the amount of creatine within muscle favorably affects muscular performance and the amount of work which can be done by the muscle. Accordingly, it is held desirable to be able to influence creatine retention in the body.

Glycogen, $(C_6H_{10}O)x$, is a carbohydrate found in animal cells and is convertible from and to glucose. Athletes endeavour to increase muscle glycogen content before competing in order to enhance muscle performance.

In this specification the term "active derivative" means anything derived from or a precursor of the relevant substance that acts in the same or similar way in the body to the substance, or which is processed into the substance when placed into the body. The terms serum and plasma can be interchanged.

According to the invention there is provided a method of increasing creatine retention in the human or animal body by causing an increase in blood plasma creatine concentration and causing a substantially simultaneous increase in blood plasma insulin concentration.

The plasma creatine concentration may be increased by ingestion and/or infusion of creatine or an active derivative thereof.

The plasma insulin concentration may be increased by infusion of insulin or an active derivative thereof and/or by the ingestion of an agent operable to cause an increase in the blood plasma insulin concentration.

The agent may be a carbohydrate or an active derivative thereof, preferably a simple carbohydrate. Preferably the carbohydrate is glucose.

Preferably the method comprises the simultaneous ingestion of creatine and an agent operable to cause an increase in the blood plasma insulin concentration substantially simultaneously with the arrival in the plasma of the creatine.

The creatine and/or the agent is preferably orally ingested.

The invention further provides a method of increasing glycogen storage, and particularly glycogen concentration in muscle of the human or animal body by causing an increase in blood plasma carbohydrate concentration and insulin concentration and causing a substantially simultaneous increase in blood plasma creatine concentration.

The plasma creatine concentration may be increased by ingestion and/or infusion of creatine or an active derivative thereof. The plasma carbohydrate, which is desirably glucose and insulin concentrations may be increased by ingestion of carbohydrate or an active derivative thereof, but desirably glucose and/or any other simple carbohydrate and/or by infusion of a carbohydrate or an active derivative thereof, such as glucose or any other simple carbohydrate.

Preferably creatine or an active derivative thereof and glucose and/or another simple carbohydrate are orally ingested.

According to the invention there is further provided a composition for increasing creatine retention in the human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof.

Preferably the composition is in the nature of a dietary supplement.

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

According to the invention there is also provided a method of increasing creatine retention in the human or animal body by ingestion and/or injection of a composition as hereinbefore described. Preferably the composition is ingested in an amount of 100 g to 700 g per day. Which may be taken in four equal parts througbout the day.

Further according to the present invention there is provided a composition for increasing creatine retention in the human or animal body, the composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

Further according to the present invention there is provided a composition for increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle, the composition comprising creatine or an active derivative tbereof together witb insulin or an active derivative thereof.

The composition may be in a form to be ingested and/or injected into the body.

According to the invention there is also provided a method of increasing creatine retention in the human or animal body by ingestion and/or injection of a composition as described above.

According to a further aspect of the invention there is provided a method increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle by ingestion and/or injection of a composition as described above.

Preferably a carbohydrate, or an active derivative thereof, is also ingested and/or injected desirably such that an increase in blood plasma carbohydrate concentration and insulin concentration occurs substantially simultaneously with an increase in blood plasma creatine concentration.

According to the invention there is also provided a composition for increasing glycogen storage in the animal or human body and particularly glycogen concentration in muscle of the human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof.

Preferably the composition is in the nature of a dietary supplement.

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

According to the invention there is also provided a method of increasing glycogen storage in the human or animal body and particularly glycogen concentration in muscle by ingestion and/or injection of a composition as hereinbefore described.

Preferably the composition is ingested in an amount of 100 g to 700 g per day, which may be taken in four equal parts throughout the day.

According to the invention there is further provided a composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use as an active pharmaceutical composition.

The invention also provides a composition comprising creatine or an active derivative thereof and insulin or an active derivative thereof for use as an active pharmaceutical preparation. The composition may also comprise a carbohydrate or an active derivative thereof.

The invention further provides creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use in the manufacture of a substance for increasing creatine retention in the human or animal body.

The invention also provides a composition comprising creatine or an active derivative thereof, and insulin or an active derivative thereof, for use in the manufacture of a substance for increasing creatine retention and/or glycogen storage in the human or animal body, such as muscle. Carbohydrate or an active derivative thereof may also be provided.

The invention further provides a composition comprising creatine or an active derivative thereof and a carbohydrate or an active derivative thereof for use in the manufacture of a substance for increasing glycogen concentration in muscle of the human or animal

Preferably the carbohydrate is glucose and/or another simple carbohydrate.

The composition preferably comprises 2 to 8% by weight creatine and 92 to 98% by weight glucose and/or another simple carbohydrate.

The methods and compositions of the invention may be used to increase bodily creatine retention in humans. This is desired, for example, by sportsmen and athletes to avoid or delay the onset of muscular fatigue. The ability to increase creatine retention may also be desired in individuals having relatively low general creatine levels, for example vegetarians who do not take animal protein, and sufferers of disease which affects muscle. The present invention enables creatine retention to be increased to a greater extent than is achieved by making creatine available to the body alone.

The invention also permits the increase of muscle glycogen concentration. This is desired by athletes to enhance performance. Also, increasing the glycogen concentration in muscle is of interest where insulin sensitivity of the body is impaired by, for example, obesity, diabetes, heart failure or post-surgical trauma.

BRIEF DESCRIPTION OF THE DRAWINGS

The invention will be further described for the purposes of illustration only with reference to the following examples and to the drawings, in which:

FIG. **1** is a graph showing increase in total creatine concentration against change in glycogen concentration in subjects of group A of Example 2;

FIG. **2** is a similar graph for subjects of group B of Example 2;

FIG. **3** is a graph showing serum insulin concentration against time for all groups in Example 4; and

FIG. **4** is a graph showing blood plasma glucose concentration against time, for all groups in Example 4.

EXAMPLE 1

Experimental

16 men were randomly divided into groups 1 (6 members), 2 (6 members) and 3 (4 members). On day one, fasted subjects gave a blood sample and then consumed the following preparations:

Group 1–5 g creatine in 250 ml low calorie hot orange

Group 2–5 g creatine in 250 ml low calorie hot orange plus 500 ml of a glucose drink (LUCOZADE(™) manufactured by Smith Kline Beecham), containing 90–100 g simple sugars.

Group 3–250 ml of low calorie hot orange

Arterialized-venous blood samples were then obtained at 20 minute intervals for the next 4½ hours, while subjects remained in a supine position. For the remainder of the day, and throughout day two, subjects ingested the mentioned preparations at 4 hourly intervals, representing a total daily creatine dose of 20 g. On the morning of day three the subjects reported back to the laboratory and underwent the same procedures as on the first day. All subjects weighed and recorded their dietary intake throughout the study, subjects in group 2 consuming a prescribed high carbohydrate diet, and undertook 24 hour urine collections on day one and day three. Plasma and urine creatine were measured using high performance liquid chromatography and serum insulin was measured using a radioimmunoassay technique.

Results

The results are shown in Table 1, in which CR=creatine. Plasma creatine concentration (u mol/l) was plotted against time for each group, and the area under each curve was determined. Urinary creatine (g) and peak serum insulin (mIU/l) were also determined.

Plasma creatine concentrations peaked within 90 minutes of creatine ingestion and declined towards resting values during the remaining 180 minutes of the 4½ hour period. The area under the plasma creatine curve was lower in group 2 than in group 1, as was urinary creatine content. Following carbohydrate ingestion, serum insulin levels peaked within 30 minutes in group 2 and returned to the pre-ingestion concentration over the remaining 240 minutes. Plasma insulin concentration did not change in group 1 or group 3 over the course of the experiment.

TABLE 1

	Group 1		Group 2	
	Mean	SE	Mean	SE
Day 1				
Area under plasma CR (umol/l/min)	2834.1	298.1	883.9**	109.9
Urinary CR (g)	9.5	1.2	5.0*	0.8
Peak serum insulin (mIU/l)	7.8	1.3	72.0**	11.2
Day 3				
Area under plasma CR (umol/l/min)	2637.5	228.6	948.3*	454.5
Urinary CR (g)	11.9	1.1	5.7*	1.2
Peak serum insulin (mIU/l)	9.5	2.0	84.2**	11.5

*P < 0.05; *P < 0.01; **P < 0.001 - significantly different from corresponding value.

The reduced area under the plasma creatine curve and the lower urinary creatine content of those subjects which had ingested creatine and carbohydrate compared with those

which had ingested only creatine shows that bodily uptake of creatine is greater in the second group. This increase in creatine uptake is believed to be insulin mediated, the plasma insulin concentration being increased by the ingested carbohydrate.

EXAMPLE 2

Experimental

A muscle biopsy sample was taken from the vastus lateralis muscle of each of 21 healthy males and was frozen in liquid nitrogen for subsequent biochemical analysis. Beginning the following day, 12 subjects (group A) each ingested 5 g of creatine dissolved in hot sugar-free orange juice, four times a day for 5 days. The remaining 9 subjects (group B) proceeded as group A, but in addition consumed 500 ml of LUCOZADE, 30 minutes after each creatine preparation had been ingested. Subjects returned the day after the 5th day of supplementation and further muscle biopsy samples were taken. 24 hour urinary collections were made prior to the first biopsy sample (control) and on the first day of creatine supplementation (day 2). Urinary creatine content (in grams) was then measured using high performance liquid chromatography.

Results

Table 2 shows the muscle concentration (mmol/kg dry mass, mean +S.E.M.) of phosphorylated creatine (PCr) non-phosphorylated creatine (Cr) and total creatine (TCr) before and after creatine supplementation. Significant differences between the groups are indicated by an asterisk $p<0.05$.

TABLE 2

	Before Creatine Supplementation	After Creatine Supplementation
	PCr	
Group A	85.1 ± 2.5	92.4 ± 2.1
Group B	84.4 ± 3.8	99.4 ± 2.6*
	Cr	
Group A	36.4 ± 1.7	49.8 ± 1.5
Group B	39.0 ± 2.3	57.1 ± 3.4*
	TCr	
Group A	121.5 ± 3.1	142.2 ± 2.6
Group B	123.4 ± 4.3	156.4 ± 5.4*

The increase in total creatine concentration after supplementation in group B was approximately 60% greater than that in group A. This increase comprises increases in both phosphorylated and non-phosphorylated creatine. Urinary creatine content was greater in group A than in group B on day 2 but there was no difference between the groups on the control day.

These results indicate that carbohydrate ingestion increases uptake of creatine in muscle in man, and to a far greater extent than to that seen when creatine alone is ingested.

EXAMPLE 3

The muscle samples obtained in the study of Example 2 were additionally analysed for muscle glycogen concentration. Muscle samples from a further group C containing 8 subjects were also analysed. This group has followed a similar regime to groups. A and B but ingested a preparation of carbohydrate but no creatine, in the form of 500 ml LUCOZADE, at same times as subjects of Groups A and B.

Table 3 shows the muscle concentration (mmol/kg) of glycogen before and after supplementation, and also the difference in the concentration.

TABLE 3

	before supplementation	after supplementation	difference
Group A			
mean	364.8	366.1	1.2
sd	63.4	65.8	67.9
se	19.1	19.8	20.5
Group B			
mean	331.1	488.7	157.6
sd	32.5	125.4	126.8
se	10.8	41.8	42.3
Group C			
mean	337.5	413.3	75.8
sd	37.3	55.9	33.2
se	13.2	19.8	11.7

sd = standard deviation, se = standard error

Table 3 shows that the mean glycogen difference after supplementation in Group A, who took creatine only, was very small.

The subjects of Group C, who took glucose only, showed an increase in muscle glycogen concentration after supplementation. However, a more marked increase in muscle glycogen concentration was shown by Group B, who took creatine and glucose together. The results of individual subjects in Group B varied greatly. However, referring to FIG. 2 it is shown that there was a linear relationship between the increase in creatine concentration and the increase in glycogen concentration in subjects of this group, showing a synergistic effect. No such relationship was observed in the subjects in Group A, who ingested only creatine (FIG. 1).

EXAMPLE 4

Experimental

Twenty nine fasted subjects were divided randomly into three groups, group A (12 subjects), group B (9 subjects) and group C (8 subjects). Each member of group A ingested 5 g of creatine dissolved in hot sugar-free orange juice. Each member of group B ingested 5 g of creatine dissolved in hot sugar-free orange juice along with 500 ml of LUCOZADE, 30 minutes after the creatine preparation had been ingested. Group C ingested 500ml of LUCOZADE alone.

Arterialised-venous blood samples were obtained from each member of each group before ingestion and at 20 minute intervals immediately following ingestion for the following 220 minutes, while subjects remained in a supine position. Blood serum insulin concentration was measured in each sample, and the results are shown in Table 4 below. Serum insulin concentration (mIU/l) was plotted against time (mins) for each group and is shown in FIG. 3.

The whole blood glucose concentration was also measured before ingestion and at 20 minute intervals for the following 280 minutes and the results obtained are shown in Table 5 below. Whole blood glucose (mmol/l) was plotted against time (mins) for each group and is shown in FIG. 4.

TABLE 4

Gp	Time (min)	Plasma Insulin (mIU/l, mean ± SEM) 0	20	40	60	120	220
A	Creatine	5.8 ± 0.8	7.3 ± 1.2	6.5 ± 1.0	6.3 ± 1.6	4.7 ± 0.3	4.7 ± 0.4
B	Creatine + carbohydrate	8.8 ± 2.0	148.7 ± 14.7	79.7 ± 9.3	51.5 ± 13.7	18.6 ± 6.0	8.2 ± 2.4
C	Carbohydrate	8.0 ± 1.5	87.6 ± 11.1	90.2 ± 20.4	60.8 ± 12.1	15.6 ± 5.2	5.8 ± 0.5

TABLE 5

Gp	Time (min)	Plasma Glucose (mmol/l, mean ± SEM) 0	20	40	60	80	100
A	Creatine	4.6 ± 0.2	4.5 ± 0.1	4.5 ± 0.1	4.5 ± 0.1	4.4 ± 0.1	4.2 ± 0.1
B	Creatine + carbohydrate	4.8 ± 0.2	8.5 ± 0.3	7.9 ± 0.2	6.6 ± 0.1	5.8 ± 0.5	5.7 ± 0.3
C	Carbohydrate	4.7 ± 0.2	8.4 ± 0.2	8.2 ± 0.2	7.7 ± 0.1	6.9 ± 0.0	6.7 ± 0.1

Gp	Time (min)	120	140	160	180	200	220	240	280
A	Creatine	4.4 ± 0.2	4.4 ± 0.1	4.3 ± 0.1	4.2 ± 0.1	4.2 ± 0.1	4.2 ± 0.2	4.3 ± 0.1	4.3 ± 0.1
B	Creatine + carbohydrate	4.8 ± 0.2	4.5 ± 0.1	4.1 ± 0.1	4.3 ± 0.2	4.3 ± 0.2	4.2 ± 0.2	4.6 ± 0.2	4.2 ± 0.1
C	Carbohydrate	5.8 ± 0.1	5.3 ± 0.3	4.6 ± 0.2	4.2 ± 0.1	4.0 ± 0.2	4.1 ± 0.2	4.3 ± 0.1	4.4 ± 0.1

The results shown in Table 4 and FIG. 3 clearly show that when creatine is ingested along with carbohydrate (group B), the serum insulin concentration is considerably greater than that found when creatine (group A) and carbohydrate (group C) are ingested alone.

Further, the results shown in Table 5 and FIG. 4, clearly show that when creatine and carbohydrate (group B) are ingested together, there is a considerably more rapid decline in blood plasma glucose concentration, than when carbohydrate is ingested alone. This is a direct result of the augmented release of insulin into the blood caused by the ingested creatine and glucose composition.

This rapid decline in blood plasma glucose concentration is indicative of an increased uptake of glucose into muscle for glycogen synthesis (as seen in Example 3). In other words, the ingestion, or infusion, of creatine in conjunction with carbohydrate increases muscle glycogen storage.

Modifications may be made within the scope of the invention. In particular the carbohydrate may be varied, for example by the use of another simple carbohydrate such as a di-or trisaccharide, although glucose is preferred because of the rapidity with which it enters the bloodstream after ingestion, causing substantially simultaneous peaks in blood insulin and creatine concentrations, and to maximise plasma insulin increase. The creatine, glucose and/or insulin or active derivatives of any of these may be infused into the blood in any suitable manner, for example by injection.

Further, the carbohydrate may be substituted or accompanied by insulin or an active derivative thereof. Ingestion or injection of compositions comprising creatine (or an active derivative thereof) and insulin (or an active derivative thereof) may be complimented by ingestion of carbohydrate, such as glucose, for example in the form of a drink. The timing of ingestion or injection (infusion) of the composition and carbohydrate is such that the increase in blood plasma carbohydrate concentration and insulin concentration and plasma creatine concentration peak substantially simultaneously.

Whilst endeavouring in the foregoing Specification to draw attention to those features of the invention believed to be of particular importance it should be understood that the Applicant claims protection in respect of any patentable feature or combination of features hereinbefore referred to and/or shown in the drawings whether or not particular emphasis has been placed thereon.

What is claimed is:

1. A method of increasing creatine retention in a human or animal body comprising causing an increase in blood plasma creatine concentration and causing a substantially simultaneous increase in blood plasma insulin concentration.

2. The method according to claim 1 comprising increasing the plasma creatine concentration by ingestion of creatine or an active derivative thereof.

3. The method according to claim 1 comprising increasing the plasma creatine concentration by infusion of creatine or an active derivative thereof.

4. The method according to claim 1 comprising increasing the plasma insulin concentration by infusion of insulin or an active derivative thereof.

5. The method according to claim 1 comprising increasing the plasma insulin concentration by ingestion of an agent operable to cause an increase in the blood plasma insulin concentration.

6. The method according to claim 5 wherein the agent is a carbohydrate or an active derivative thereof.

7. The method according to claim 5 wherein the agent is a simple carbohydrate.

8. The method according to claim 7 wherein the simple carbohydrate is glucose.

9. The method according to claim 5 wherein at least one of the creatine and the agent is orally ingested.

10. The method according to claim 1 comprising increasing the blood plasma creatine concentration by administering creatine or an active derivative thereof and increasing the blood plasma insulin concentration by administering a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative.

11. The method according to claim 10 wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

12. The method according to claim 1 comprising ingesting creatine and an agent operable to cause an increase in the blood plasma insulin concentration substantially simultaneously with the arrival in the plasma of the creatine.

13. A method of increasing glycogen storage in a human or animal body comprising causing an increase in blood plasma carbohydrate concentration and insulin concentration and causing a substantially simultaneous increase in blood plasma creatine concentration.

14. The method according to claim 13 comprising increasing the plasma creatine concentration by administering creatine or ao active derivative thereof by at least one of ingestion and infusion.

15. The method according to claim 13 comprising increasing the plasma carbohydrate and insulin concentrations by administering a carbohydrate or an active derivative thereof by at least one of ingestion and infusion.

16. The method according to claim 13 comprising increasing the plasma glucose and insulin concentrations by infusion of a carbohydrate or an active derivative thereof, the carbohydrate being selected from the group consisting of glucose and other simple carbohydrates.

17. The method according to claim 13 comprising orally ingesting creatine or an active derivative thereof and a carbohydrate or an active derivative thereof, the carbohydrate being selected from the group consisting of glucose and other simple carbohydrates.

18. The method according to claim 13 comprising increasing the blood plasma creatine concentration by administering creatine or an active derivative thereof and increasing the blood plasma insulin concentration by administering a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative.

19. The method according to claim 18 wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

20. A composition for use in a human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative, and the amount of the creatine or its derivative and the amount of the carbohydrate or its derivative are effective to increase creatine retention in the body.

21. The composition according to claim 20 wherein the composition is in the nature of a dietary supplement.

22. The composition according to claim 20 wherein the carbohydrate is selected from the group consisting of glucose and other simple carbohydrates.

23. The composition according to claim 20 wherein the composition comprises in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

24. The composition according to claim 20 wherein the amount of the creatine or its derivative and the amount of the carbohydrate or its derivative are effective to increase glycogen storage in the body.

25. A method of increasing creatine retention in a human or animal body comprising administering a composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof by at least one of ingestion and injection, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative.

26. The method according to claim 25 wherein the composition is ingested in an amount of 100 g to 700 g per day.

27. The method according to claim 25 wherein the composition is administered in four equal parts throughout the day.

28. The method according to claim 25 wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% aod the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

29. The method of claim 25 wherein the carbohydrate is selected from the group consisting of glucose and other simple carbohydrates.

30. A composition for use in a human or animal body comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

31. The composition according to claim 30 wherein the creatine or its derivative and the insulin or its derivative are present in amounts effective to increase glycogen storage in the body.

32. The composition according to claim 30 wherein the creatine or its derivative and the insulin or its derivative are present in amounts effective to increase creatine retention in the body.

33. The composition according to claim 30 wherein the composition is in a form that can be administered by at least one of ingestion and injection.

34. 8 The composition according to claim 30 further comprising a carbohydrate or an active derivative thereof.

35. A method of increasing creatine retention in a human or animal body comprising administering a composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof by at least one of ingestion and injection.

36. A method according to claim 35 further comprising administering a carbohydrate or an active derivative thereof such that an increase in blood plasma carbohydrate concentration and insulin concentration occurs substantially simultaneously with an increase in blood plasma creatine concentration.

37. A method of increasing glycogen storage in a human or animal body comprising administering a composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof by at least one of ingestion and injection.

38. A method according to claim 37 further comprising administering a carbohydrate or an active derivative thereof such that an increase in blood plasma carbohydrate concentration and insulin concentration occurs substantially simultaneously with an increase in blood plasma creatine concentrations.

39. A method of increasing glycogen storage in the human or animal body comprising administering a composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof by at least one of ingestinn and infusion, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative.

40. A method according to claim 39 wherein the composition is ingested in an amount of 100 g to 700 g per day.

41. A method according to claim 39 wherein the composition is administered in four equal parts throughout the day.

42. The method according to claim 39 wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative present in an amount ranging from 92 to 98%.

43. The method according to claim 39 wherein the carbohydrate is selected from the group consisting of glucose and other simple carbohydrates.

44. A pharmaceutical having a composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in the amount by weight which is greater than an amount of the creatine or its derivative, and the amount of said creatine or its derivative and the amount of said carbohydrate or its derivative are effective to increase creatine retention in the body.

45. A pharmaceutical having a composition comprising creatine or an active derivative thereof together with insulin or an active derivative thereof.

46. The pharmaceutical according to claim 45 wherein the composition further comprises a carbohydrate or an active derivative thereof in an amount by weight which is greater than an amount of the creatine or its derivative.

47. A composition for use in a human or animal body, the composition comprising creatine or an active derivative thereof together with a carbohydrate an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative, and the amount of said creatine or its derivative and the amount of said carbohydrate or its derivative are effective to increase glycogen storage in the body.

48. The composition according to claim 47 wherein the composition is in the nature of a dietary supplement.

49. The composition according to claim 47 wherein the carbohydrate is selected from the group consisting of glucose and other simple carbohydrates.

50. The composition according to claim 47, wherein the composition comprises, in % by weight based upon a total weight of the composition: the creatine or its derivative present in an amount ranging from 2 to 8% and the carbohydrate or its derivative in an amount ranging from 92 to 98%.

51. The composition according to claim 47 wherein the amount of said creatine or its derivative and the amount of said carbohydrate or its derivative are effective to increase creatine retention in the body.

52. A pharmaceutical having a composition comprising creatine or an active derivative thereof together with a carbohydrate or an active derivative thereof, wherein the composition comprises the carbohydrate or its derivative in an amount by weight which is greater than an amount of the creatine or its derivative, and the amount of the creatine or its derivative and the amount of the carbohydrate or its derivative are effective to increase glycogen storage in the body.

53. A composition for use in a human or animal body comprises, in % by weight based upon a total weight of the composition: creatine or its derivative present in an amount ranging from 2 to 8% and a carbohydrate or its derivative in an amount ranging from 92 to 98%.

* * * * *

UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO.: 5,968,900

DATED: October 19, 1999

INVENTOR(S): Paul Leonard Greenhaff

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

Title page, item

[30] Foreign Application Priority Data

Aug. 17, 1994 [GB] United Kingdom.....9425514.8

Signed and Sealed this

Twelfth Day of September, 2000

Attest:

Q. TODD DICKINSON

Attesting Officer

Director of Patents and Trademarks

EXHIBIT

C

US006277396B1

(12) **United States Patent**
Dente

(10) **Patent No.: US 6,277,396 B1**
(45) **Date of Patent: Aug. 21, 2001**

(54) **DIETARY SUPPLEMENT CONTAINING A THERMOGENIC SUBSTANCE AND AN ADRENAL SUPPORT SUBSTANCE**

(75) Inventor: **Gerard Dente**, Cedar Grove, NJ (US)

(73) Assignee: **Maximum Human Performance, Inc.**, Cedar Grove, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/568,587**

(22) Filed: **May 11, 2000**

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(52) **U.S. Cl.** **424/439**; 424/434; 424/436; 424/489; 424/451; 424/725; 424/728; 514/966; 514/772.4

(58) **Field of Search** 424/436, 439, 424/725

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(57) **ABSTRACT**

A dietary supplement system having a daytime component and a nighttime component is provided, wherein the daytime component comprises at least one thermogenic substance and the nighttime component comprises at least one adrenal support substance.

6 Claims, No Drawings

DIETARY SUPPLEMENT CONTAINING A THERMOGENIC SUBSTANCE AND AN ADRENAL SUPPORT SUBSTANCE

FIELD OF THE INVENTION

The present invention relates to a dietary supplement comprising at least one thermogenic substance, at least one adrenal support substance and/or at least one anxiolytic substance. More particularly, the presently claimed invention relates to a dietary supplement system having daytime and nighttime components wherein the daytime component contains a thermogenic substance and the nighttime component contains an adrenal support substance.

BACKGROUND OF THE INVENTION

Dietary and nutritional supplements have become a significant element of the human diet. Most dietary supplements contain stimulants as their active ingredient. Generally, stimulants can have undesirable side effects. The most common side effect is a general "jittery" feeling, but other side effects include stress on adrenal glands, restlessness, nervousness, gastro intestinal disturbances, muscle twitching, and in some extreme cases, cardiac arrhythmia. In view of the above, dietary supplements containing stimulants are not designed for nighttime usage. Because of the stimulants, dietary supplements are formulated for daytime consumption and not recommended for nighttime usage. The present invention provides a 24-hour dietary supplement system that can be consumed for daytime and nighttime usage.

SUMMARY OF THE INVENTION

The present invention provides a dietary supplement comprising at least one thermogenic substance and at least one adrenal support substance. In one embodiment, the thermogenic substance is selected from a group consisting of caffeine, catechin, MaHuang, ephedrine, synephrine (*Citrus aurantium*), norephedrine, psuedoephedrine, and White Willow (*salicin*) and extracts thereof and mixtures thereof. For purposes of this invention, the term "thermogenic" is defined as any natural or synthetic substance, nutrient, vitamin, mineral, herb or compound used to increase metabolism and accelerate calorie expenditures. In one embodiment, the term thermogenic means heat producing or fat burning. In another embodiment, the adrenal support substance is selected from a group consisting of Cordyceps (*Cordyceps sinensis*), Ashwagandha (*Withania somniferum*), Astragalus (*Asgragalus mebranaceus*), ginseng (*Panax ginseng*), Schisandra (*Schizendra chinensis*), Siberian ginseng (*Eleutherococcus senticosus*), licorice (*Glycerrhiza glabra*), Asian ginseng, Codonopsis ("Dangshen"), Vitamin B complex, Vitamin C, adrenal glandular extract, embryo extract, chromium, Vitamin B5 (pantothenic acid) and extracts thereof and mixtures thereof. The term "adrenal support" substance is defined as any natural or synthetic substance, nutrient, vitamin, mineral, herb, or compound used to support, maintain and/or improve adrenal functions and to reduce stress.

In still another embodiment, the supplement further comprises at least one thyrogenic substance. In yet another embodiment, the thyrogenic substance is selected from a group consisting of Guggul (*Commiphora mukul*) or guggulsterones, iodine, copper, selenium, thyroid glandular extract, tyrosine, phosphates and extracts thereof and mixtures thereof. In one embodiment, the iodine sources include, but are not limited to, seaweed, kelp, seafood, shellfish, and bladderwrack (*Focus vesiculosus*). For purposes of this invention, a "thyrogenic" substance is any natural or synthetic substance, nutrient, vitamin, mineral, herb or compound used to support, maintain, and/or improve thyroid functions.

In still yet another embodiment, the supplement further comprises at least one blood sugar regulation substance. In a further embodiment, the blood sugar regulation substance is selected from a group consisting of Bitter Melon (*Momordica charantia*), vanadium, allano lactone, Fenugreek (*Trigonella foenumgraecum*), garcinia (*Garcinia cambogia*), gymnema (*Gymnema sylvestra*), marshmallow (*Althaea officinalis*), chromium, chromium GTF, chromium picolinate, chromium polynicotinate, alpha lipoic acid, inula racemusa, zinc, magnesium, cyclo-hispor, Agaricus campestris (mushroom), *Medicago sativa* (Lucerna), pinitol (*Bougainvillea spectabilis*) and extracts thereof and mixtures thereof. A "blood sugar regulation" substance is defined as any natural or synthetic substance, nutrient, vitamin, mineral, herb, or compound used to regulate or manipulate blood sugar levels and/or glucose metabolism. The current US diet consist of high amounts of carbohydrates and refined sugars. This can result in elevated blood sugar levels. High levels of blood sugar can increase the production of insulin, which accelerates the storage of body fat. The blood sugar regulation substance of the present invention, functions to help stabilize normal blood sugar levels and increase the body's ability to lose stored body fat.

In still a further embodiment, the supplement further comprises at least one anxiolytic substance. An "anxiolytic" substance is defined as any natural or synthetic substance, nutrient, vitamin, mineral, herb or compound used as a calming agent, to reduce stress and anxiety, or improve sleep. In yet a further embodiment, the anxiolytic substance is selected from a group consisting of valerian (*Valeriana officinalis*), damiana, chamomile (*Matricaria chamomila*), kava kava (*Piper methysticum*), passionflower (Passilflora spp.), hops (*Humulus lupulus*), skullcap, St. John's wort (*Hypericum perforatum*), hawthorn (*Crataegus oxyacantha*), lavender (*Lavendula officinalis*), melatonin, 5-Hydroxytrytophan and extracts thereof and mixtures thereof.

In one embodiment, the supplement further comprises at least one diuretic or water balancing substance. Normal diets contain high amounts of sodium, which can lead to excessive amounts of water retention. The water balancing substance of the present invention will help regulate and relieve excessive water retention. In another embodiment, the water balancing substance is selected from a group consisting of cranberry (*Vaccinum magrocapon*), dandelion, elder (*Sambucus nigra*, Sambucus Canadensis), horsetail (*Equisetum arvense*), uva ursi (*Arctostaphylos uva-ursi*), parsley (*Petroselinum crispum*), B-6 and extracts thereof and mixtures thereof.

In still yet a further embodiment, the present invention relates to dietary supplement system comprising a daytime component and a nighttime component, said daytime component comprising at least one thermogenic substance and said nighttime component comprising at least one adrenal support substance. In another embodiment, the system is a 24-hour system. In still another embodiment, the thermogenic substance is selected from a group consisting of caffeine, catechins (epigalocatechin-EGCG), MaHuang (8% Ephedra alkaloids) ephedrine HCl, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof. In one embodiment, the caffeine may be green tea (*Camilla sinensis*) and guarana

(methylxanthines). In yet another embodiment, the adrenal support substance is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, Vitamin B complex, pantothenic acid, Vitamin C, adrenal glandular extract, chromium and extracts thereof and mixtures thereof.

In still yet another embodiment, the daytime component further comprises at least one thyrogenic substance; the thyrogenic substance is selected from a group consisting of Guggul (guggulsterones), iodine, copper, selenium, thyroid glandular extract, tyrosine, phosphates and extracts thereof and mixtures thereof In a further embodiment, the daytime component further comprises at least one blood sugar support substance; the blood sugar support substance being selected from a group consisting of Bitter Melon, vanadium, allano lactone, Fenugreek, garcinia, gymnema, marshmallow, chromium, cbromium GTF, chromium picolinate, chromium polynicotinate, alpha lipoic acid, inula racemusa, zinc, magnesium, cyclo-hispor, *Agaricus campestris, Medicago sativa*, pinitol and extracts thereof and mixtures thereof.

In still a further embodiment, the nighttime component further comprises at least one anxiolytic substance; the anxiolytic substance is selected from a group consisting of valerian, damiana, chamomile, kava kava, passionflower, hops, skullcap, St. John's wort, hawthorn, lavender, melatonin, 5-Hydroxytrytophan and extracts thereof and mixtures thereof In still yet a further embodiment, nighttime component further comprises at least one thyrogenic substance; the thyrogenic substance being selected from a group consisting of Guggul (guggulsterones), iodine, copper, selenium, thyroid glandular extract, tyrosine and extracts thereof and mixtures thereof. In a further embodiment, the nighttime component of the system of the present invention further comprises at least one water balancing substance; the water balancing substance being selected from a group consisting of cranberry, dandelion, elder, urva ursi, parsley, B-6 and extracts thereof and mixtures thereof In yet another embodiment, the supplement comprises a water balance blend. In still another embodiment, the water balancing blend comprises the water balancing substance and other ingredients. In still yet another embodiment, the water balance blend comprises Buchu leaf, cornsilk stylus, couchgrass rhizome, hydrangea root, juniper berry, uva ursi leaf, cranberry fruit, dandelion root, artichoke leaf, and extracts thereof and mixtures thereof. In a further embodiment, the supplement further comprises calcium sulfate, gelatin, magnesium stearate, and silica.

In a further embodiment, the system further comprises at least one of following: inert diluents, granulating and disintegrating agents, binding agents, lubricating agents, plasticizers, humectants, electrolytes, buffers, colorants, aromatic agents, flavoring agents, emulsifying agents, compounding agents, formulation agents, permeation enhancers and bulking agents.

In another embodiment, the present invention relates to a dietary supplement comprising at least one thermogenic substance, at least one thyrogenic substance and at least one blood sugar support substance. In still another embodiment, the thermogenic substance being selected from a group consisting of caffeine, catechins, MaHuang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof, the thyrogenic substance being selected from a group consisting of Guggul (guggulsterones), iodine, copper, selenium, thyroid glandular extract, tyrosine and extracts thereof and mixtures thereof; and the blood sugar support substance being selected from a group consisting of Bitter Melon, vanadium, allano lactone, Fenugreek, garcinia, gymnema, marshmallow, chromium, chromium GTF, chromium picolinate, chromium polynicotinate, alpha lipoic acid, inula racemusa, zinc, magnesium, cyclo-hispor, *Agaricus campestris, Medicago sativa*, pinitol and extracts thereof and mixtures thereof.

In yet another embodiment, the supplement further comprising at least one adrenal support substance, the adrenal support substance is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, Vitamin B complex, pantothenic acid, Vitamin C, adrenal glandular extract, chromium and extracts thereof and mixtures thereof.

In still yet another embodiment, the supplement further comprises at least one anxiolytic substance, the anxiolytic substance is selected from a group consisting of valerian, damiana, chamomile, kava kava, passionflower, hops, skullcap, St. John's wort, hawthorn, lavender, melatonin, 5-Hydroxytrytophan and extracts thereof and mixtures thereof.

In a further embodiment, the present invention relates to a method of manufacturing a dietary supplement with daytime and nighttime components, said method comprising: formulating a daytime component comprising at least one thermogenic substance and a nighttime component comprising at least one adrenal support substance; the thermogenic substance is selected from a group consisting of caffeine, catechins, MaHuang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof; the adrenal support substance is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, Vitamin B complex, pantothenic acid, Vitamin C, adrenal glandular extract, cbromium and extracts thereof and mixtures thereof. In still a further embodiment, the method further comprises utilizing the supplement as a fat burning composition.

In yet a further embodiment, the presently claimed invention relates to a fat burning dietary supplement having daytime and nighttime components, said supplement comprising a daytime component comprising at least one thermogenic substance and a nighttime component comprising at least one anxiolytic substance. In still yet a further embodiment, the thermogenic substance is selected from a group consisting of caffeine, catechins, MaHuang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof. In another embodiment, the anxiolytic substance is selected from a group consisting of valerian, damiana, chamomile, kava kava, passionflower, hops, skullcap, St. John's wort, hawthorn, lavender, melatonin, 5-Hydroxytrytophan and extracts thereof and mixtures thereof. In another embodiment, the daytime component further comprises at least one adrenal support substance. In a further embodiment, the nighttime component comprises at least one adrenal support substance. In still a further embodiment, the adrenal support substance is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, Vitamin B complex, pantothenic acid, Vitamin C, adrenal glandular extract, chromium and extracts thereof and mixtures thereof.

DETAILED DESCRIPTION OF THE INVENTION

As required, detailed embodiments of the present invention are disclosed herein; however, it is to be understood that

the disclosed embodiments are merely exemplary of the invention that may be embodied in various forms. Therefore, specific structural and functional details disclosed herein are not to be interpreted as limiting, but merely as a basis for the claims and as a representative basis for teaching one skilled in the art to variously employ the present invention.

The present invention relates to a 24-hour dietary supplement system having a daytime component and a nighttime component and related methods of manufacturing the same. In one embodiment, the daytime component comprises a thermogenic substance and the nighttime component comprises an adrenal support substance. The thermogenic substance of the daytime component of the system of the present invention functions as a fat burner, metabolism booster and/or weight loss aid. The fat burning effects of the thermogenic decreases over time and places stress upon the adrenal glands. The adrenal support substance of the nighttime component functions to support the adrenal glands and maintain effective thermogenic fat burning. In one embodiment, the nighttime components may be consumed after about 4 to about 12 hour intervals of consuming the daytime component.

In another embodiment, the thermogenic substance of the daytime component comprises a guarana seed extract (contains naturally occurring caffeine), Ma haung herb extract, and White Willow bark extract. In one embodiment, White Willow bark functions as a catalyst that enhances the effect of the stimulants or thermogenic substance. In another embodiment, the thermogenic substance of the present invention is tea extract, specifically, green tea extract. Tea is derived from *Camellia sinensis*, a plant native to China. Green tea is the most common beverage in many Asian countries. Green tea has been shown to reduce body fat by promoting fat oxidation, exhibit thermogenic properties, and provide other health benefits, including helping control body composition. The active ingredients in the green tea are caffeine and catechin polyphenols. Studies have shown that the active thermogenic ingredient in the green tea extract is the catechins (epigallocatechins-EGCG).

A thermogenic substance is a substance that increases caloric expenditure. The most commonly used thermogenics are caffeine and Ma Huang. These thermogenic compounds may have stimulatory effects. In one embodiment, the thermogenic substance of the present invention may act as stimulants and the stimulants employed in the supplement of the present invention, is a methylxanthine, or mixtures of methylxanthines. The most widespread stimulant is caffeine, which is primarily ingested by drinking tea or coffee. Caffeine affects the central nervous system, mainly the cerebrum. Caffeine is found in coffee beans, tea, cola nuts, guarana, cacao seeds, and mate. Mate is made from a South American evergreen tree (*Ilex paraguariensis*) whose leaves contain caffeine. Mate is customarily consumed as a tea-like beverage. Guarana is a vine that climbs trees in South America, and grows as a shrub when cultivated in the open. The botanical name is *Paullinia cupana* H.B.K., variety sorbilis. Seeds cultivated from the plant yield guaranine, which has the same chemical composition as caffeine. A syrup extract is obtained from the seeds and used in soft drinks, or the seeds can be roasted and ground into powder. Caffeine may also be manufactured synthetically. The chemical name for caffeine is 1,3,7-trimethylxanthine. Other common methylxanthine stimulants include 1,3-trimethylxanthine (found in tea and commonly called theophylline), and 3,7-dimethylxanthine (found in cacao seeds and tea, and commonly called theobromine). Products containing caffeine are ubiquitous. Ma Huang is an herb that contains ephedra-alkaloids (ephedrine). Ephedra has a thermogenic fat burning effect and increases caloric expenditure. Research has shown that caffeine and ephedra work synergistically to further increase thermogenesis. Thermogenesis is the process by which the increase in body temperature increases caloric expenditure.

In still another embodiment, the adrenal support substance of the nighttime component comprises chromium as chromium picolinate, licorice root extract, Siberian ginseng root extract, Asian ginseng root and astragalus root. Ginseng includes active ingredients such as saponins termed ginsenosides, essential oils, phytosterol, carbohydrates, amino acids, peptides, vitamins, minerals and other ingredients. During stressful situations, the adrenal glands release corticosteroids and adrenaline. When these hormones are depleted, the organism reaches an exhaustive phase. Adrenal support substances, such as ginseng, delay the exhaustive phase and allow a more economical and efficient release of these hormones. Adrenal support substances also reduce stress. In another embodiment, the adrenal support substance includes adaptogens, such as (chick) embryo extract. Adaptogens are substances that help the body respond and adapt to stress by normalizing bodily functions that have been disrupted by various types of stress. Other than the brain, the most important target organ for adaptogens is the adrenal glands. The adrenal glands are a target organ because the glands produce various hormones (adrenaline, noradrenaline, androgens,estrogens, glucocorticoids and mineralcorticoids) and because of their overriding influence on metabolism and other aspects of the physical and mental functions. As stated above, the use of thermogenics have negative effects on the adrenal glands. If the adrenal functions are depleted, the resulting mental irritation, loss of muscle and regression of strength may take a long time to recover and recoup. One of the functions of the adrenal support substance of the nighttime component of the system of the present invention is to normalize adrenal functions and to revitalize the adrenal glands from the stressful effects placed upon the glands from the consumption of the thermogenic substance in the daytime component. If you can normalize adrenal hormone output, virtually all physiological functions improve-from sex and sleep to immune response. For bodybuilding purposes, normalizing adrenal output can increase the potential for fat loss and muscle growth.

In yet another embodiment, the daytime component further comprises a thyrogenic substance and a blood sugar support substance. In still yet another embodiment, the thyrogenic substance comprises a blend of guggulsterones extract of Commiphora mukul resin, bladderwrack kelp, Atlantic kelp, and sargassi seaweed. Guggul is a resin from a tree native to India. This resin has been used in Ayurvedic medicine, which combined it with other plant products to cleanse and rejuvenate the body, especially the blood vessels and joints. It was also used for sore throats and digestive complaints. In Chinese medicine, guggul is known as mo yao and is used to activate blood flow, relieve pain and speed recovery. Guggul is also known to lower cholesterol and increase thyroid functions and the production of thyroid hormones. The active ingredients in guggul include essential oils, myrcene, Z and E guggulsterones, alpha-campborene, various other guggulsterones, and makulol. The Z and E guggulsterones, extracted with ethyl acetate, are the constituents that appear to be responsible for lowering blood lipids. In another embodiment, the thyrogenic substance may also include selenium as selenomethionine and copper as copper gluconate. The thyrogenic substance also provides

weight loss control benefits. Dieting and caloric restrictions slow down human metabolism and the thyroid gland functions to regulate metabolism. The thyrogenic substance supports the thyroid functions and increases the metabolism, thereby increasing the burning of body fat.

In a further embodiment, the blood sugar support substance comprises garcinia cambogia fruit extract, gymnema sylvestre leaf and chromium as chromium picolate.

In still a further embodiment, the nighttime component comprises an anxiolytic substance, in particular, kava kava root. An anxiolytic substance is a relaxant, and the most widespread used relaxant is kava. The anxiolytic substance of the present invention, functions to help improve sleep which is often compromised when dieting or taking supplements to increase metabolism. Kava, which is also known as kava-kava, yaquona, ava, ava-ava, awa, or kawa, is a member of the pepper family Piperceae. Kava is obtained from the rhizome and roots of Piper methysticum Forst. Kava is the most relaxing botanical herb with the exception of the opium poppy. Kava is known to induce general relaxation in humans when orally ingested, but it does not cause drowsiness or involuntary sleep. A liquid macerate of the kava root has been used on islands in the South Pacific in social gatherings and religious rituals for over three thousand years.

Recently, kava has been scientifically scrutinized and its psychoactive ingredients identified. These ingredients are referred to as kavalactones. A total of fifteen kavalactones have been identified to date, including kavain (a.k.a. kawain), dihydrokavain (a.k.a. dihydrokawain), methysticin, dihydromethysticin, yangonin, and demethoxyyangonin. A synthetic version of kava, known as D, L-kavain is also available. The specific kavalactones in kava root extract vary depending upon the origin of the kava plant. Kava roots, and their rhizomes, or distal root tips, are preferred, but other parts of the plant may be used. High quality extracts of kava are sold based upon the total kavalactone content, rather than upon analysis of the individual lactones contained therein.

Studies indicate that kavalactones can relieve nervous anxiety, tension, restlessness, as well as promote muscle relaxation. Studies have also shown that consumption of kavalactones does not impair neurophysiological activity, as evidenced by measurements of recognition rates, and driving ability. Further, kavalactones are nonaddictive and do not induce involuntary sleep or symptoms of drunkenness.

Traditionally, kava root is prepared for human consumption by pulverizing the root and/or rhizome and mixing it with water to obtain a liquid which can be consumed orally. Presently, kava root extracts are manufactured using ethanol, as a solvent, as the kavalactones are readily soluble in ethanol. The extracted material is a yellowish brown paste or powder, which is tested to determine the weight percentage of kavalactones. Synthetic versions of kava are also available.

In still a further embodiment, the nighttime component may include one or more of the following: a thyrogenic substance, a cleansing blend and/or a water balancing blend. In another embodiment, the thyrogenic substance of the nighttime component comprises a thyrogenic blend of guggulsterone extracts, Atlantic kelp, bladderwrack kelp, and sargassi seaweed. In still yet a further embodiment, the cleansing blend comprises Senna leaf, rhubarb root, cascara sagrada bark, apple fruit, cassia powder, St. John's bread, tamarind fruit, date fruit and fig fruit. In a further embodiment, the water balancing blend comprises Buchu leaf, cornsilk stylus, couchgrass rhizome, hydrangea root, juniper berry, uva ursi leaf, cranberry fruit extract, dandelion root extract, and artichoke leaf extract.

The supplement of the present invention may be formulated for administration to any suitable human by any conventional route such as oral, rectal, topical or nasal. Any carriers known in the art for oral application may be used. For solid form preparation, such as, for example, powders, tablets, disbursable granules and capsules, a solid carrier may be one or more substances such as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, tablets disintegrating agents, encapsulating materials and the like. Suitable carrier materials may include, for example, magnesium carbonate, calcium carbonate, sodium bicarbonate, magnesium stearate, calcium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, cellulose derivatives, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, alginates, gelatin, polyvinyl pyrrolidone, polyethyl glycols, quaternary ammonium compounds and the like.

Liquid form preparations include solutions, suspensions and emulsions. Suitable carriers may include, for example, water, coloring, flavoring agents, stabilizers and thickening agents. Viscous materials, such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose and other agents known to the pharmaceutical art may also be used.

The composition to be administered may be prepared in accordance with any dose preparation method known in the art, for example mixing, encapsulation, etc., and is not limited. The components of the composition may be added in any order without limitation.

For rectal applications, suitable formulations for compositions according to the present invention include suppositories (emulsion or suspension type), and rectal gelatin capsules (solution or suspensions). In a typical suppository formulation, the active ingredients are combined with an appropriate pharmaceutically acceptable suppository base such as cocoa butter, esterified acids, glycerinated gelatin, and various water soluble or dispersable bases like polyethylene glycols and polyoxyethylene glycols and polyoxyethylene sorbitan fatty acid esters.

Numerous modifications and variations of the present invention are possible in light of the above teachings. It is therefore to be understood that within the scope of the attendant claims attached hereto, this invention may be practiced otherwise than as specifically disclosed herein.

What is claimed is:

1. A dietary supplement comprising at least one thermogenic substance, at least one adrenal support substance and at least one thyrogenic substance, wherein said thermogenic substance is selected from a group consisting of caffeine, catechins, Mallluang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof, wherein said adrenal support substance is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, adrenal glandular extract, embryo extract, and extracts thereof and mixtures thereof, and said thyrogenic substance is selected from a group consisting of guggelsterones, thyroid glandular extract, tyrosine and extracts thereof and mixtures thereof.

2. A dietary supplement comprising at least one thermogenic substance, at least one adrenal support substance and at least one blood sugar regulation substance, wherein

said thermogenic substance is selected from a group consisting of caffeine, catechins, MaHuang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof, wherein said adrenal support substance is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, adrenal glandular extract, embryo extract, and extracts thereof and mixtures thereof, and wherein said blood sugar regulation substance is selected from a group consisting of Bitter Melon, vanadium, allano lactone, Fenugreek, garcinia, gymnema, marshmallow, alpha lipoic acid, inula racemusa, cyclo-hispor, *Agaricus campestris, Medicago sativa*, pinitol and extracts thereof and mixtures thereof.

3. A dietary supplement system comprising a daytime component and a nighttime component, said daytime component comprising at least one thermogenic substance and at least one thyrogenic substance, and said nighttime component comprising at least one adrenal support substance, said thermogenic substance of said daytime component is selected from a group consisting of caffeine, catechins, MaHuang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof, said thyrogenic substance of said daytime component is selected from a group consisting of guggulsterones, thyroid glandular extract, tyrosine and extracts thereof and mixtures thereof, and said adrenal support substance of said nighttime component is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, adrenal glandular extract, embryo extract and extracts thereof and mixtures thereof.

4. A dietary supplement system comprising a daytime component and a nighttime component, wherein said daytime component comprising at least one thermogenic substance and at least one blood sugar support substance, and said nighttime component comprising at least one adrenal support substance, said thermogenic substance of said daytime component is selected from a group consisting of caffeine, catechins, MaHuang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof, said blood sugar support substance of said daytime component being selected from a group consisting of Bitter Melon, vanadium, allano lactone, Fenugreek, garcinia, gymnema, marshmallow, alpha lipoic acid, inula racemusa, cyclo-hispor, *Agaricus campestris, Medicago sativa*, pinitol and extracts thereof and mixtures thereof, and said adrenal support substance of said nighttime component is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, adrenal glandular extract, embryo extract and extracts thereof and mixtures thereof.

5. A dietary supplement system comprising a daytime component and a nighttime component, said daytime component comprising at least one thermogenic substance, and said nighttime component comprising at least one adrenal support substance and at least one thyrogenic substance, said thermogenic substance of said daytime component is selected from a group consisting of caffeine, catechins, MaHuang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof, said adrenal support suhstance of said nighttime component is selected from a group consisting of Cordyceps, Ashwagandha, Astragalus, ginseng, Schisandra, Siberian ginseng, licorice, Asian ginseng, Codonopsis, adrenal glandular extract, embryo extract and extracts thereof and mixtures thereof, and said thyrogenic substance of said nighttime component is selected from a group consisting of guggulsterones, thyroid glandular extract, tyrosine and extracts thereof and mixtures thereof.

6. A dietary supplement comprising at least one thermogenic substance, at least one thyrogenic suhstance and at least one blood sugar support substance, wherein said thermogenic substance being selected from a group consisting of caffeine, catechins, MaHuang, ephedrine, synephrine, norephedrine, psuedoephedrine, and White Willow and extracts thereof and mixtures thereof, said thyrogenic substance being selected from a group consisting of guggulsterones, thyroid glandular extract, tyrosine and extracts thereof and mixtures thereof, and said blood sugar support substance being selected from a group consisting of Bitter Melon, vanadium, allano lactone, Fenugreek, garcinia, gymnema, marshmallow, alpha lipoic acid, inula racemusa, cyclo-hispor, *Agaricus campestris, Medicago sativa*, pinitol and extracts thereof and mixtures thereof.

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EXHIBIT

2

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

IOVATE HEALTH SCIENCES U.S.A., INC., et al. ~~IOVATE HEALTH SCIENCES INTERNATIONAL, INC., IOVATE T & P, INC.,~~ ~~FLAMMA SpA,~~ ~~and USE TECHNO CORPORATION,~~ Plaintiffs, v. WELLNX LIFE SCIENCES INC ~~(d/b/a NV Inc.)~~, et al. ~~NXCARE INC.,~~ ~~NXLABS INC.,~~ ~~SLIMQUICK LABORATORIES,~~ ~~BIOGENETIX,~~ ~~DEREK WOODGATE, and~~ ~~BRADLEY WOODGATE,~~ Defendants.	~~Civil Action No.~~ C.A. No. 07-286 JJF JURY TRIAL DEMANDED

FIRST AMENDED COMPLAINT

Plaintiffs Iovate Health Sciences U.S.A., Inc. ("Iovate U.S.A."), Iovate Health Sciences International, Inc. ("Iovate International"), and Iovate T & P, Inc. ("Iovate T & P") (collectively "Iovate"~~), Flamma SpA ("Flamma") and Use Techno Corporation ("UTC") (collectively~~ or "Plaintiffs"), hereby allege for their Complaint against WellNx Life Sciences Inc. ("WellNx") (d/b/a NV Inc.), NxCare Inc. ("NxCare"), NxLabs Inc. ("NxLabs"),~~ Slimquick Laboratories~~

~~("Slimquick"),~~ Biogenetix, Derek Woodgate and Bradley Woodgate (collectively "Defendants"), on personal knowledge as to their own activities and on information and belief as to all other matters, as follows:

PARTIES

1. Iovate U.S.A. is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 3880 Jeffrey Boulevard, Blasdell, New York, NY, 14129.

2. Iovate International is a corporation organized and existing under the laws of Ontario, Canada, with its principal place of business at ~~5100 Spectrum Way, Mississauga~~381 North Service Road West, Oakville, ON, Canada, ~~L4W 5S2.~~L6M 0H4.

3. Iovate T & P is a corporation organized and existing under the laws of Ontario, Canada, with its principal place of business at ~~5100 Spectrum Way, Mississauga, ON, Canada. L4W 5S2.~~381 North Service Road West, Oakville, ON, Canada, L6M 0H4.

~~4. Flamma is a corporation organized and existing under the laws of Italy, with its principal place of business at Via Bedeschi 22 24040 Chignolo d'Isola, Italy.~~

~~5. UTC is a company with its principal place of business at 1-27 Sasaoshinmachi, Fukuchiyama-shi, Kyoto, Japan 620-0055.~~

4. ~~6.~~ Upon information and belief, Defendant WellNx is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9, and/or 218 Silvercreek Parkway, Guelph, ON, Canada.

5. ~~7.~~ Upon information and belief, Defendant NxCare is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

6. ~~8.~~ Upon information and belief, Defendant NxLabs is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

~~9. Upon information and belief, Defendant Slimquick is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.~~

7. ~~10.~~ Upon information and belief, Defendant Biogenetix is a corporation organized and existing under the laws of Ontario, Canada, with a place of business at 1680 Tech Avenue, Unit 1, Mississauga, ON, Canada, L4W 5S9.

8. ~~11.~~ Upon information and belief, Defendants Derek Woodgate and Bradley Woodgate are individuals and the founders of WellNx, (and its predecessor entities), NxCare, NxLabs, ~~Slimquick,~~ Biogenetix, and are officers, shareholders, and/or directors of WellNx, NxCare, NxLabs, ~~Slimquick,~~ Biogenetix, and personally direct and control the activities herein complained.

9. ~~12.~~ Upon information and belief, Defendant Derek Woodgate resides at 1594 Waldie Avenue, Milton, ON, Canada, L9T 5K8.

10. ~~13.~~ Upon information and belief, Defendant Bradley Woodgate resides at 803-373 Front Street West, Toronto, ON, Canada, M5V-3R7.

JURISDICTION AND VENUE

11. ~~14.~~ This is an action for patent infringement arising under the patent laws of the United States, Title 35 of the United States Code. Accordingly, this Court has subject matter jurisdiction pursuant to 28 U.S.C. §§ 1331 and 1338.

12. ~~15.~~ Venue is proper in this Court pursuant to 28 U.S.C. §§ 1331, 1391(b), 1391(d) and 1400.

13. ~~16.~~ Upon information and belief, Defendant WellNx maintains an office at 1201 N. Orange Street, Suite 741, Wilmington, DE, 19801.

14. ~~17.~~ Upon information and belief, Defendant NxCare maintains an office at 874 Walker Rd., Dover, DE, 19904.

GENERAL ALLEGATIONS

15. ~~18.~~ On October 26, 1999, United States Patent No. 5,973,199 ("the '199 patent"), titled "Hydrosoluble Organic Salts of Creatine," was duly and legally issued by the United States Patent and Trademark Office. A true and correct copy of the '199 patent is attached as Exhibit A of this Complaint.

~~19. Flamma is the owner and assignee of the '199 patent.~~

16. ~~20.~~ Iovate Health Sciences U.S.A., Inc. is the ~~exclusive licensee~~owner through assignment of the '199 patent.

~~21. On April 6, 2004, United States Patent No. 6,716,459 ("the '459 patent"), titled "Composition for Inhibiting Increase of Blood Sugar Level or Lowering Blood Sugar Level," was duly issued by the United States Patent and Trademark Office. A true and correct copy of the '459 patent is attached as Exhibit B of this Complaint.~~

~~22. UTC granted an exclusive license to Iovate International, and its affiliates, for the entire scope of the claims of the '459 patent.~~

17. ~~23.~~ On October 19, 1999, United States Patent No. 5,968,900 ("the '900 patent"), titled "Increasing Creatine and Glycogen Concentration in Muscle," was duly issued by the United States Patent and Trademark Office. A true and correct copy of the '900 patent is attached as Exhibit ~~C~~B of this Complaint.

18. ~~24.~~ Iovate T & P is the owner of all rights, title and interest in and to the '900 patent.

19. On August 21, 2001, United States Patent No. 6,277,396 ("the '396 patent"), titled "Dietary Supplement Containing a Thermogenic Substance and an Adrenal Support Substance," was duly and legally issued by the United States Patent and Trademark Office. A true and correct copy of the '396 patent is attached as Exhibit C of this Complaint.

20. Iovate T & P is the owner through assignment of the '396 patent.

21. ~~25.~~ Upon information and belief, Defendants have made, used, offered for sale, sold and/or imported nutritional supplements, including ~~Slimage, Slimquick Night~~, Vaso, Vaso XP, Hyper Growth, Lean Hyper Growth, Muscle Expansion Pack, ~~Aminovol,~~ Pump System, ~~and/or~~ Creatine-D^2T, REVxp Hardcore, Methyl Ripped, Ripped System and/or NV throughout the U.S. and in this judicial district.

~~26. The product label for the Slimage product lists "Lagerstroemia Speciosa (leaf) (standardized for 5% corosolic acid)".~~

~~27. The product label for the Slimquick Night product lists "Banabo extract (Lagerstroemia Speciosa) (leaf) Standardized for 5% Corosolic Acid)".~~

~~28. The supplement facts for the Hypergrowth product lists "Corosolic acid" as an ingredient.~~

22. The supplement information for Vaso lists "Tri-creatine malate."

23. The supplement information for Vaso XP lists "Tri-creatine malate."

24. The supplement information for Hypergrowth lists 10 grams of creatine derivatives (micronized creatine monohydrate, tricreatine malate and buffered creatine), and "InsuTech." "Each serving of Hypergrowth delivers 10g of CreaPlex3 . . . for maximum creatine absorbtion and retention."

25. The supplement information for Lean Hypergrowth lists 10 grams of creatine derivatives (micronized creatine monohydrate, tricreatine malate and buffered creatine) and "InsuTech."

26. ~~29.~~ The supplement ~~facts for the Aminovol product lists "Corosolic acid" as an ingredient.~~information for Muscle Expansion Pack (Anavol, Vaso) lists "Tri-creatine malate."

27. The supplement information for Pump System (Vaso, Plasmavol, NO Surge) lists "Tri-creatine malate."

28. ~~30.~~ The product label for Creatine-D^2T lists 4000 mg of Creatine derivatives (Creatine Ethyl Ester, Creatine AKG, and Creatine Decanoate) per serving, and an "Insulin Signaling Complex".

29. ~~31.~~ The supplement information for ~~Hypergrowth lists 10 grams of creatine derivatives (micronized creatine monohydrate, tricreatine malate and buffered creatine), and "InsuTech." "Each serving of Hypergrowth delivers 10g of CreaPlex3 . . . for maximum creatine absorption and retention."~~REVxp Hardcore lists caffeine anhydrous, 70 % total catechins, ginsing, and 4-hydroxyisoleusine (from fenugreek)(seed).

30. The supplement information for Methyl Ripped lists di-caffeine alpha ketoglutarate, di-caffeine malate, esterified green tea extract (standardized for 45% 45% Epigallocatechin Gallate (EGCG) Ester, 2% Epicatechin Gallate (ECG) Ester, 2% Gallocatechin Gallate (GCG) Ester, 1% Catechin Gallate (CG) Ester), Gugglesterones E&Z HCl, and Ashwagandha.

31. The supplement information for Ripped System (Methyl Ripped, Methyl Dry) lists di-caffeine alpha ketoglutarate, di-caffeine malate, esterified green tea extract (standardized for 45% 45% Epigallocatechin Gallate (EGCG) Ester, 2% Epicatechin Gallate (ECG) Ester, 2% Gallocatechin Gallate (GCG) Ester, 1% Catechin Gallate (CG) Ester), Gugglesterones E&Z HCl, and Ashwagandha.

32. The supplement information for NV lists Green Tea Extract (Leaf)(Standardized for polyphenols and Epigallocatechin Gallate (EGCG)), Panax Ginseng Extract, and Alpha-Lipoic Acid.

FIRST CAUSE OF ACTION
(Infringement of the '199 Patent)

33. ~~32.~~ Plaintiffs repeat and re-allege the allegations of paragraphs 1-~~31~~32 of the Complaint as if set forth herein.

34. ~~33.~~ By their actions, Defendants have infringed and are infringing the '199 patent.

35. ~~34.~~ Upon information and belief, the infringement by Defendants has been and continues to be willful.

36. ~~35.~~ As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

~~**SECOND CAUSE OF ACTION**~~
~~**(Infringement of the '459 Patent)**~~

~~36. Plaintiffs repeat and re-allege the allegations of paragraphs 1-35 of the Complaint as if set forth herein.~~

~~37. By their actions, Defendants have infringed and are infringing the '459 patent.~~

~~38. Upon information and belief, the infringement by Defendants has been and continues to be willful.~~

~~39. As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.~~ **~~THIRD~~ CAUSE OF ACTION**

(Infringement of the '900 Patent)

37. ~~40.~~ Plaintiffs repeat and re-allege the allegations of paragraphs 1-~~39~~36 of the Complaint as if set forth herein.

38. ~~41.~~ By their actions, Defendants infringed and are infringing the '900 patent.

39. ~~42.~~ Upon information and belief, the infringement by Defendants has been and continues to be willful.

40. ~~43.~~ As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

THIRD CAUSE OF ACTION
(Infringement of the '396 Patent)

41. Plaintiffs repeat and re-allege the allegations of paragraphs 1-40 of the Complaint as if set forth herein.

42. By their actions, Defendants infringed and are infringing the '396 patent.

43. Upon information and belief, the infringement by Defendants has been and continues to be willful.

44. As a result of Defendants' acts of infringement, Plaintiffs have suffered and will continue to suffer damages in an amount to be proved at trial.

PRAYER FOR RELIEF

WHEREFORE, Plaintiffs pray for entry of judgment against each Defendant as follows:

A. The Defendants infringe the '199, '~~459.~~900 and '~~900~~396 patents by their making, using, offering for sale, selling and/or importing nutritional supplements, including Vaso and/or Vaso XP, Hyper Growth, Lean Hyper Growth, Muscle Expansion Pack, Pump System, ~~Slimage.~~

~~Slimquick Night, Aminovol and~~ Creatine-D^{2}T, REVxp Hardcore, Methyl Ripped, Ripped System and NV;

B. That Defendants' infringement of the '199, '~~459.~~900 and '~~900~~396 patents is willful;

C. That Defendants, their officers, directors, affiliates, agents, servants, employees and attorneys, and all those persons acting in privity or in concert with any of them, be preliminarily and permanently enjoining from infringement of the '199, '~~459.~~900 and '~~900~~396 patents;

D. That Plaintiffs be awarded their damages for infringement of the '199, '~~459.~~900 and '~~900~~396 patents, and that the damages be trebled;

E. That this case be declared to be exceptional in favor of Plaintiffs under 35 U.S.C. § 285, and that Plaintiffs be awarded their costs, attorneys' fees, and other expenses incurred in connection with this action;~~ and~~

F. That Plaintiffs be awarded such other and further relief as may be appropriate.

DEMAND FOR JURY TRIAL

Plaintiffs demand a trial by jury.

Dated: ~~May 24, 2007~~January 25, 2008

Respectfully submitted,

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